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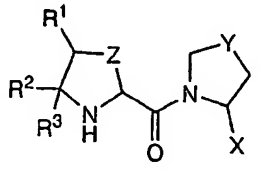
(54) Title: PYRROLIDINE, THIAZOLIDINE AND OXAZOLIDINE COMPOUNDS WHICH INHIBIT DIPEPTIDYL PEPTIDASE-IV (DPP)



(I)

(57) Abstract: A compound of the formula (I) or a pharmaceutically acceptable salt thereof: [wherein X is cyano or H; Y is CH?2#191, O, S, SO or SO?2# Z is (lower)alkylene, and the like; R¿1? and R¿2? are linked together to form (lower)alkylene or (lower)alkenylene, and R¿3? is H, (lower)alkyl or hydroxy; and the like; and the (lower)alkylene formed by R¿1? and R¿2? and the like may be substituted which may be substituted.] Compounds of formula (I) inhibit DPP-IV activity. They are therefore useful in the treatment of conditions mediated by DPP-IV, such as NIDDM.

DESCRIPTION

PYRROLIDINE,THIAZOLIDINE AND OXAZOLIDINE COMPOUNDS WHICH INHIBIT DIPEPTIDYL PEPTIDASE-IV (DPP IV)

TECHNICAL FIELD

This invention relates to the compound and pharmaceutically acceptable salt thereof which inhibit dipeptidyl peptidase-IV (DPP-IV).

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above-mentioned compound or pharmaceutically acceptable salt thereof as an active ingredient, a method for treatment and/or prevention of NIDDM, or the like, and use of the above compound.

BACKGROUND ART

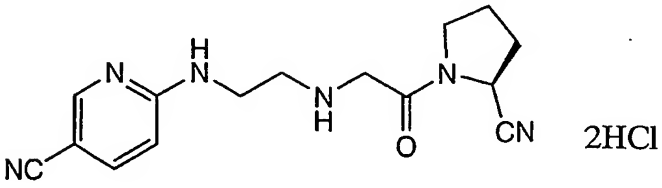
It is known that DPP-IV has various physiological functions in living body, especially has the action which inactivates Glucagon-like peptide-1 (GLP-1) by cleaving the terminal dipeptide (His-Ala). That is, the resultant peptide is the receptor antagonist of GLP-1 and totally reduces the activity of GLP-1.

This GLP-1 has very important role in sugar metabolism. For example, (1) GLP-1 intensifies the secretion of insulin, (2) express genes which are indispensable for the secretion of insulin, (3) stimulate proliferation of β-cell, (4) suppresses secretion of glucagon, (5) suppresses the function about secretion and motility of digestive organs (especially, peristalsis), and (6) suppresses appetite. That is, GLP-1 restricts food ingestion, postpones the process of digestion and absorption, and raised the use of the sugar in blood.

Therefore, the inhibitor of DPP-IV can maintain the activity of GLP-1, so it is expected as a medicine to treat and prevent various diseases, especially non-insulin

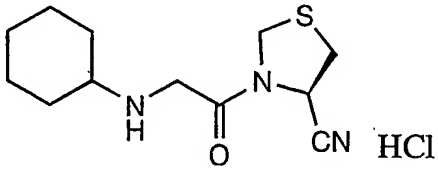
dependent diabetes mellitus (NIDDM).

Hitherto, such inhibitors of DPP-IV are known so far. For example, in US 6,011,155, 2-cyanopyrrolidine compounds like following are disclosed.



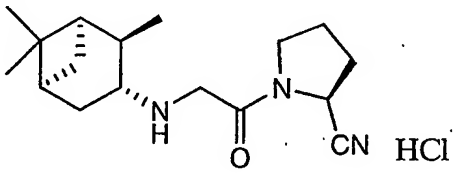
Pyrrolidine, 1-[[2-[(5-cyano-2-pyridinyl)amino]ethyl]amino]actyl-2-cyano, (S)-, monohydrochloride

In US 6,110,949, 4-cyanothiazolidine compounds like following are disclosed.



3-[(Cyclohexyl)amino]acetyl-4-cyano-(R)-thiazolidine monohydrochloride

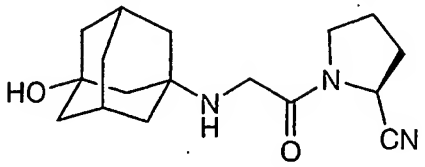
In US 6,124,305, 2-cyanopyrrolidine compounds like following are disclosed.



Pyrrolidine, 1-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano, (S)[1S[1α,2β,3α(S),5α]] monohydrochloride

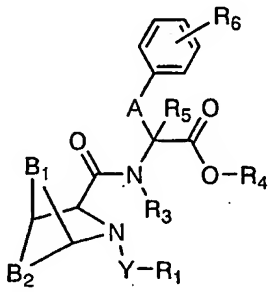
In WO 00/34241, 2-cyanopyrrolidine compounds like following are disclosed.

WO 02/02556 discloses following compounds as α4



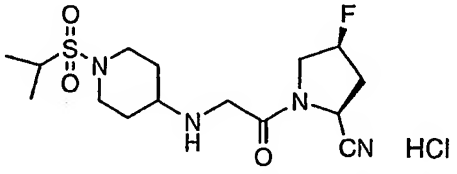
"LAF-237"
Pyrrolidine, 1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano, (S)

integrin receptor antagonists for treating integrin mediated disorder such as asthma, rheumatoid arthritis, or the like.



In the above formula, R_3 and R_5 may be bonded to form a pyrrolidine ring. However, such compound or compounds, which has hydrophilic group on azabicyclo moiety, are not described specifically.

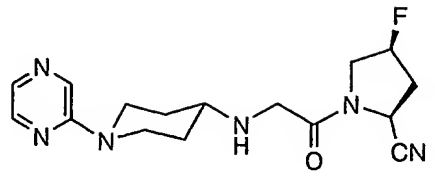
WO 03/002553 discloses (2S,4S)-4-fluoro-1-({[1-(isopropylsulfonyl)-4-piperidinyl]amino}acetyl)-2-pyrrolidinecarbonitrile hydrochloride.



However, the other pyrrolidinecarbonitrile compounds substituted by [(lower)alkyl]sulfonyl group are not described.

WO 03/074500 discloses (2S,4S)-4-fluoro-1-(2-{[1-(2-pyrazinyl)piperidin-4-yl]amino}acetyl)-2-pyrro

lidinecarbonitrile.



DISCLOSURE OF INVENTION

Under the above situation, the inventors of this invention found that the compound of this invention has remarkable activity to inhibit DPP-IV, and completed this invention.

Accordingly, this invention relates to DPP-IV inhibitor. More particularly, this invention relates to DPP-IV inhibitor useful for treating or preventing conditions mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

That is, one object of this invention is to provide new compound and pharmaceutically acceptable salt thereof, of which activity to inhibit DPP-IV is remarkably improved against known compounds. Further, the object of this invention is to provide a method for producing the new compound.

Another object of this invention is to provide a medicament and pharmaceutical composition containing the compound(s) and/or pharmaceutically acceptable salts thereof as an active ingredient.

A further object of this invention is to provide a method for inhibiting DPP-IV comprising administering an effective amount of the compound and/or pharmaceutically acceptable salt thereof.

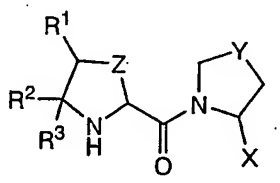
A further object of this invention is to provide a

use of the compound and pharmaceutically acceptable salt thereof as medicaments.

A further object of this invention is to provide the compound and pharmaceutically acceptable salt thereof which are useful for the manufacture of medicaments for treating or preventing conditions mediated by DPP-IV inhibition, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus, especially NIDDM.

A further object of this invention is to provide the commercial package comprising the pharmaceutical composition containing the new compound.

The compound of this invention can be represented by the following formula (I):



(I)

[wherein

X is cyano or H;

Y is CH_2, O, S, SO or SO_2;

Z is (lower)alkylene (which may be substituted with R^4), O, S, SO or SO_2;

R^1 and R^2 each is independently H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; R^3 is (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; and R^4 is hydroxy or hydroxy[(lower)alkyl]; or

R^1 and R^2 are linked together to form (lower)alkylene or (lower)alkenylene; R^3 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; and R^4 is hydroxy or hydroxy[(lower)alkyl]; or

R^1 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; R^2 and R^3 are linked together to form (lower)alkylene or (lower)alkenylene; and R^4 is hydroxy or hydroxy[(lower)alkyl]; or

R^1 and R^4 are linked together to form (lower)alkylene or (lower)alkenylene; R^2 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; and R^3 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl];

the (lower)alkylene or (lower)alkenylene formed by R^1 and R^2, R^2 and R^3, or R^1 and R^4 may be substituted; and

the substituent(s) on the (lower)alkylene or (lower)alkenylene is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy, hydroxy[(lower)alkyl], oxo, [(lower)alkane]sulfonylamide and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl, aryl (which may be substituted) or heteroaryl (which may be substituted));

the substituent(s) on the aryl or heteroaryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy and hydroxy[(lower)alkyl].]

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Therefore, the "(lower)alkylene" means a straight or branched chain aliphatic hydrocarbon divalent group, such as methylene, methylmethylene, ethylmethylene, isopropylmethylene, isobutylmethylene, tert-butylmethylene, ethylene, methylethylene, ethylethylene, isopropylethylene, isobutylethylene,

tert-butylethylene, propylene, methylpropylene, ethylpropylene, isopropylpropylene, and the like.

The "(lower)alkenylene" means a straight or branched chain aliphatic hydrocarbon divalent group having at least one C-C double bond, such as ethenylene, methylethenylene, ethylethenylene, isopropylethenylene, isobutylethenylene, tert-butylethenylene, propenylene, methylpropenylene, ethylpropenylene, isopropylpropenylene, 1-butenylene, 2-butenylene, 2-pentenylene, 3-pentenylene, and the like.

In the case where Z is (lower)alkylene, it is preferably (C1-C4)alkylene, more preferably (C1-C3)alkylene, more preferably (C1-C2)alkylene, most preferably methylene. In such a case, Z ((lower)alkylene) may be substituted with R^4, and preferably -CH(R^4)-.

In the case where R^1 and R^2 or R^1 and R^4 are linked together to form (lower)alkylene, it is preferably (C1-C4)alkylene, more preferably (C2-C4)alkylene, more preferably (C3-C4)alkylene, most preferably tetramethylene. In the case where R^2 and R^3 are linked together to form (lower)alkylene, it is preferably (C2-C5)alkylene, more preferably (C3-C5)alkylene, more preferably (C4-C5)alkylene, most preferably pentamethylene. In these cases, R^1, R^2 (or R^4) and the carbon atoms connected with R^1 or R^2 (or R^4) (or R^2, R^3 and the carbon atom connected with R^2 and R^3) form cycloalkyl.

The "cycloalkyl" means (C3-C10)cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, and it is preferably cyclopentyl or cyclohexyl, more preferably cyclohexyl.

In the case where R^1 and R^2 or R^1 and R^4 are linked together to form (lower)alkenylene, it is preferably (C1-C4)alkenylene, more preferably (C2-C4)alkenylene,

most preferably 2-butenylene. In the case where R^2 and R^3 are linked together to form (lower)alkenylene, it is preferably (C2-C5)alkenylene, more preferably (C3-C5)alkenylene, more preferably (C4-C5)alkylene, most preferably 2- or 3-pentenylene. In these cases, R^1, R^2 (or R^4) and the carbon atoms connected with R^1 or R^2 (or R^4) (or R^2, R^3 and the carbon atom connected with R^2 and R^3) form cycloalkenyl.

The "cycloalkyl" means (C4-C10)cycloalkyl group, such as cyclobutenyl, cyclopentenyl, cyclohexeyl, cycloheptyl, and the like, and it is preferably cyclopenteyl or cyclohexeyl, more preferably cyclohexeyl.

The "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, and it is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "hydroxy[(lower)alkyl]" means the (lower)alkyl group substituted by hydroxy group, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxy-tert-butyl, hydroxypentyl, hydroxyhexyl, and the like, and it is preferably hydroxy[(C1-C4)alkyl], more preferably hydroxy[(C1-C2)alkyl], most preferably hydroxymethyl.

The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, and the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most preferably methoxy.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, it is preferably a chlorine atom.

The "[(lower)alkane]sulfonamide" means a

sulfonamide group substituted with (lower)alkyl group mentioned above on the sulfonyl group, such as methanesulfonamide, ethanesulfonamide, propanesulfonamide, isopropanesulfonamide, isobutanesulfonamide, tert-butanesulfonamide, and the like, and it is preferably [(C1-C4)alkane]sulfonamide, more preferably [(C1-C2)alkane]sulfonamide, most preferably methanesulfonamide.

The "aryl" means an aromatic hydrocarbon group, such as phenyl, naphthyl, indenyl, or the like, and it is preferably (C6-C10)aryl, more preferably phenyl.

The "heteroaryl" means 5- or 6-membered aromatic heterocyclic group which contains at least one heteroatom such as nitrogen atom, oxygen atom and/or sulfur atom. The "heteroaryl" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl; and 6-membered heteroaryl group such as pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, and the like, and is preferably 6-membered heteroaryl, more preferably pyridinyl.

The (lower)alkylene or (lower)alkenylene may be subsutituted. The number of the substituent is preferably 1 to 4, more preferably 1 or 2, most preferably 1. In the case where the number is plural, they may be the same or different each other.

The "aryl" or "heteroaryl" may be substituted. The number of the substituent is preferably 1 to 4, more preferably 1 or 2, most preferably 1. In the case where "aryl" or "heteroaryl" has plural substituents, they may be the same or different each other, but needless to say, "aryl" or "heteroaryl" may not have substituent.

The compound of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both

mixture and separate individual isomers. However, in the 2-portion of 2-cyanopyrrolidine, (2S) isomer is more preferable.

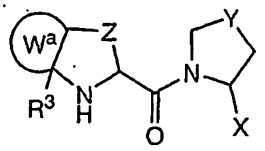
The compound of the formula (I) may also exist in tautomeric forms and this invention includes both mixture and separate individual tautomers.

The compound of the formula (I) and its salt may be in a form of a solvate such as hydrate, which is included within the scope of the present invention.

Further, included in the scope of invention is radiolabelled derivative of compound of formula (I) which is suitable for biological studies.

The compound of this invention can be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, or the like.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, or the like.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, or the like.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, or the like.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, or the like.), a salt with an amino acid (e.g., arginate, aspartate, glutamate, or the like.), or the like.

The compound (I) may preferably include;
condensated compounds of the formula (Ia)



(Ia)

[wherein

X is cyano or H;

Y is CH_2, O, S, SO or SO_2;

Z is (lower)alkylene (which may be substituted with R^4), O, S, SO or SO_2;

W^a is cycloalkyl or cycloalkenyl which may be substituted;

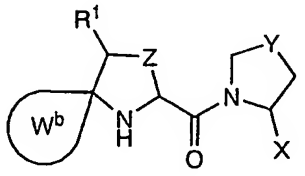
R^3 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl];

R^4 is hydroxy or hydroxy[(lower)alkyl];

the substituent(s) on the cycloalkyl or cycloalkenyl is(are) selected form the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy, hydroxy[(lower)alkyl] oxo, [(lower)alkane]sulfonylamide and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl, aryl (which may be substituted) or heteroaryl (which may be substituted));

the substituent(s) on the aryl or heteroaryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy and hydroxy[(lower)alkyl].],

spiro compounds of the formula (Ib)



(Ib)

[wherein

X is cyano or H;

Y is CH_2, O, S, SO or SO_2;

Z is (lower)alkylene (which may be substituted with R^4), O, S, SO or SO_2;

W^b is cycloalkyl which may be substituted;

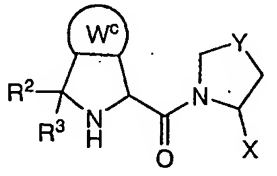
R^1 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl];

R^4 is hydroxy or hydroxy[(lower)alkyl];

the substituent(s) on the cycloalkyl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy, oxo, [(lower)alkane]sulfonylamide and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl), hydroxy[(lower)alkyl], aryl (which may be substituted) or heteroaryl (which may be substituted));

the substituent(s) on the aryl or heteroaryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy and hydroxy[(lower)alkyl].], and

condensated compounds of the formula (Ic)



(Ic)

[wherein

X is cyano or H;

Y is CH_2, O, S, SO or SO_2;

W^c is cycloalkyl or cycloalkenyl which may be substituted;

R^2 and R^3 each is independently H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl];

the substituent(s) on the cycloalkyl or cycloalkenyl is(are) selected form the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy, hydroxy[(lower)alkyl] oxo, [(lower)alkane]sulfonylamide and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl, aryl (which may be substituted) or heteroaryl (which may be substituted));

the substituent(s) on the aryl or heteroaryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano,

nitro, amino, hydroxy and hydroxy[(lower)alkyl].]

In the each definition of the compound formula (I), (Ia), (Ib) and (Ic), preferably,

(1) X is cyano,

(2) X is H,

(3) Y is CH_2,

(4) Y is S,

(5) Z is (C1-C2)alkylene,

(6) Z is methylene,

(7) R^1 and R^2 are linked together to form (lower)alkylene (W^a is cycloalkyl which may be substituted), R^3 and R^4 is H,

(8) R^1 and R^2 are linked together to form (C1-C4)alkylene (W^a is (C3-C6)cycloalkyl which may be substituted), R^3 and R^4 is H,

(9) R^1 and R^2 are linked together to form (C4)alkylene (W^a is cyclohexyl which may be substituted), R^3 and R^4 is H,

(10) R^1 and R^2 are linked together to form (lower)alkylene (W^a is cycloalkyl which may be substituted), R^3 is hydroxy, and R^4 is H,

(11) R^1 is H, R^2 and R^3 are linked together to form (lower)alkylene (W^b is cycloalkyl which may be substituted), and R^4 is H,

(12) R^1 is (C1-C4)alkyl, R^2 and R^3 are linked together to form (lower)alkylene (W^b is cycloalkyl which may be substituted), and R^4 is H,

(13) R^1 is (C1-C2)alkyl, R^2 and R^3 are linked together to form (lower)alkylene (W^b is cycloalkyl which may be substituted), and R^4 is H,

(14) R^1 is hydroxy, R^2 and R^3 are linked together to form (lower)alkylene (W^b is cycloalkyl which may be substituted), and R^4 is H,

(15) R^1 and R^4 are linked together to form (lower)alkylene

(W^c is cycloalkyl which may be substituted), R^2 and R^3 is H,

(16) R^1 and R^4 are linked together to form (C1-C4)alkylene (W^c is (C3-C6)cycloalkyl which may be substituted), R^3 and R^4 is H,

(17) R^1 and R^4 are linked together to form (C4)alkylene (W^c is cyclohexyl which may be substituted), R^3 and R^4 is H,

(18) the "(lower)alkylene formed by R^1 and R^2" is (C3-C4)alkylene,

(19) the "(lower)alkylene formed by R^1 and R^4" is (C3-C4)alkylene,

(20) the "(lower)alkylene formed by R^2 and R^3" is (C4-C5)alkylene,

(21) the "(lower)alkylene formed by R^1 and R^2" is tetramethylene,

(22) the "(lower)alkylene formed by R^1 and R^4" is tetramethylene,

(23) the "(lower)alkylene formed by R^2 and R^3" is pentamethylene,

(24) the "the substituent(s) on the (lower)alkylene" is(are) selected from the group consisting of carboxy, sulfonic acid, amino, hydroxy, hydroxy[(lower)alkyl], oxo, [(lower)alkane]sulfonylamide and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl, aryl (which may by substituted) or heteroaryl (which may be substituted)),

(25) the "the substituent(s) on the (lower)alkylene" is(are) selected from the group consisting of amino, hydroxy, hydroxy[(lower)alkyl] and $-NR^5R^6$ (R^5 is H or (C1-C2)alkyl; R^6 is (C1-C2)alkyl, aryl (which may by substituted) or heteroaryl (which may be substituted)),

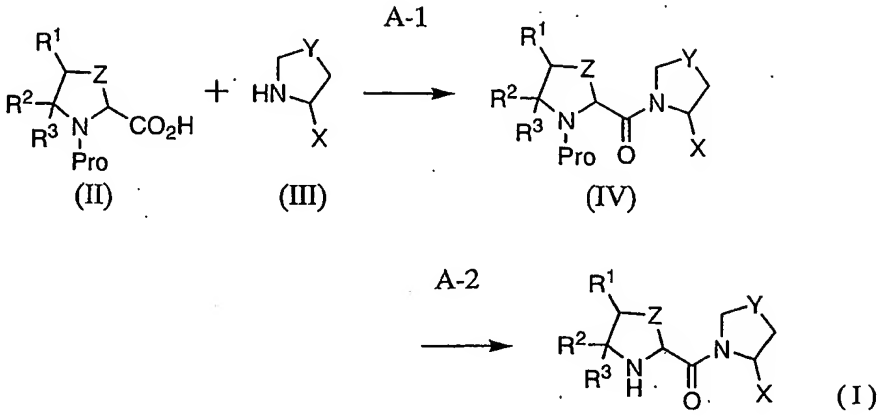
(26) the "the substituent(s) on the (lower)alkylene" is(are) hydroxy or hydroxy[(lower)alkyl],

(27) the "the substituent(s) on the (lower)alkylene" is(are) hydroxy,

(28) the "the substituent(s) on the aryl or heteroaryl" is(are) selected from the group consisting of (lower)alkyl, carboxy, halogen, amino, hydroxy and hydroxy[(lower)alkyl].

The compound of the formula (I) of the present invention can be prepared according to the following Process A.

[Process A]



In the above formula, R^1 to R^3, X, Y and Z represent the same meanings as defined above. "Pro" means the protective group of amino group.

Process A is the process for preparing the Compound (I). First, Compound (IV) is synthesized by condensation of Compound (II) and (III) (Process A-1), then Compound (IV) is deprotected to prepare Compound (I) (Process A-2).

Compound (II) and (III) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds.

Process A-1 is the process for preparing the Compound (IV) from carboxylic acid Compound (II) and amine Compound (III) in solvent.

This process can be carried out by general condensating method, for example, by using condensating agent.

In the case where condensing agent is used, the condensing agent employable in this process is not particularly limited so long as it accelerates forming amide bond and may include carbodiimide compounds such

as dicyclohexylcarbodiimide (DCC), diisopropyl-carbodiimide (DIPCI), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSCD), preferably WSCD.

In the case, base and catalyst are generally used. The base employable in this process is not particularly limited so long as it accelerates this process and may include organic amines such as triethylamine, tributylamine, diisopropylethylamine (DIEA). The catalyst employable in this process is not particularly limited so long as it can mainly make the carboxyl group of Compound (II) active and may include 1-hydroxybenzotriazole (HOBT).

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as dimethylformamide and dimethylacetamide; halogenated hydrocarbons such as methylene chloride, chloroform.

This process is generally carried out by adding the condensing agent and catalyst to the suspension or solution of Compound (II) and (III). Further, base is added to the mixture preferably dropwise.

The temperature at that time varies depending on the starting material, the solvent, or the like, but it is usually from -10℃ to 20℃. After adding, the temperature is preferably raised to room temperature.

The reaction time after the adding base varies depending on the starting material, the solvent, or the like, but it is usually from 1hr to 30hrs.

After the reaction, the mixture is partitioned between water and organic solvent insoluble with water such as ethyl acetate, chloroform, or the like, and organic layer is separated. The organic layer is washed by water, hydrochloric acid, saturated sodium hydrogencarbonate solution, brine, or the like, dried over anhydrous

magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, or the like.

Then, Compound (IV) is deprotected to obtain Compound (I).

Concerning the protective group of Compound (II) and (IV), the general kind and the condition of cleavage reaction may be referred to 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC.

For example, in the case where "Pro" is carbamate such as tert-butoxycarbonyl or methoxycarbonyl, the cleavage reaction is carried out by acidic condition.

The solvent employable in this case is not particularly limited so long as it is inactive in this reaction and may include ethers such as diethylether, tetrahydrofuran, 1,4-dioxane.

The reagent for making acidic condition is not particularly limited so long as it accelerates cleavage reaction and may include hydrogen chloride solution in above mentioned solvent such as 4N hydrogen chloride solution in 1,4-dioxane.

This process is generally carried out by adding the reagent for making acidic condition dropwise to the solution of compound (IV). The temperature at that time varies depending on the starting material, the solvent, or the like, but it is usually from -10℃ to 20℃, preferably room temperature. After adding, the temperature is preferably raised to room temperature.

The reaction time after the adding the reagent for making acidic condition varies depending on the starting material, the solvent, or the like, but it is usually from 1hr to 12hrs, preferably from 1hr to 5hrs.

After the reaction, the mixture is concentrated in

vacuo, basified with basic aqueous solution such as saturated aqueous sodium hydrogencarbonate, and extracted with organic solvent insoluble with water such as ethyl acetate, chloroform, or the like. The organic layer is washed by aqueous solvent such as brine, dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound (I) may be obtained by conventional purifying method such as thin layer chromatography, silica gel column chromatography. However, after the reaction of Process A-2, the residue may be only washed with solvent, which does not dissolve the target Compound (I).

To the cycloalkyl group or cycloalkenyl group formed by linking R^1 and R^2, R^2 and R^3, or R^1 and R^4, hydroxy group can be stereoselectively introduced by bio-conversion. For example, Compound (I) and (IV) not having hydroxy group on cycloalkyl group or cycloalkenyl group can be hydroxylated by actinomycetes as follows.

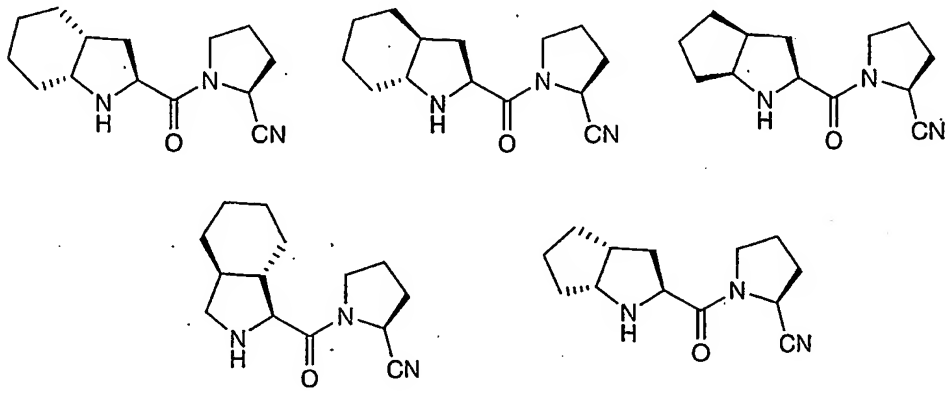
(1) First, actinomycetes is fermented. The kind of actinomycetes can be selected according to the desired position or conformation of hydroxy group. Alternatively, the mixture of compound having various hydroxy group position or conformation can be obtained by certain kind of actinomycetes. In such case, desired compound can be purified by conventional method such as HPLC.

As actinomycetes, for example, *Nonomuraea reseoviolacea* JCM-3145 can be used. Actinomycetes is generally incubated 20 to 40℃ for 2 to 7 days in or on appropriate medium. The optimal condition for fermentation can be selected according to the kind of actinomycetes.

(2) Then, the solution of substrate is added to the broth

of actinomycetes.

As substrate, Compound (I) and (IV) can be used. For example, the following compounds or protected compounds thereof can be used as substrate of the hydroxylation by actinomycetes.



The solvent employable in this reaction is not particularly limited so long as it is inactive in this reaction and may include water; alcohol such as methanol and ethanol; and mixed solvent thereof.

The reaction can be generally carried out at 20 to 40℃ with stirring for 2 to 7days. The progress of the reaction can be monitored by HPLC. After the reaction, hydroxylated compound can be purified by conventional method such as HPLC.

Above processes, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method. For example of making hydrochloride or trifluoroacetate, to the compound, the solution of acid such as 4N hydrochloride/dioxane or trifluoroacetic acid is added, then the solvent and excess acid is removed and the reside is triturated appropriate solvent such as diethlether.

In the above compounds, which have reactive group, may be protected at the group on cue and be deprotected on cue. In these reactions (protecting or deprotecting

steps), concerning the kind of protective group and the condition of the reaction, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. may be referred.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless otherwise such changes and modifications depart from the scope of the present invention hereinafter defined, they should be construed as being included therein.

Example 1-1

tert-Butyl (2S,3aS,6R,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate

1-Hydroxybenzotriazole (276mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (345mg) were added to an ice-cooled suspension of (2S)-2-pyrrolidinecarbonitrile hydrochloride (217mg) and (2S,3aS,6R,7aS)-1-(tert-butoxycarbonyl)-6-hydroxyoctahydro-1H-indole-2-carboxylic acid (467mg) in N,N-dimethylformamide (20mL). Triethylamine (0.456mL) was added dropwise and the mixture was stirred at the same temperature for 1hr. The mixture was warmed to room temperature and stirred for 23hrs.

The resulting mixture was partitioned between water and ethyl acetate. The organic layer was washed with 0.5N hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (SiO_2: 25g, eluent: ethyl acetate/n-hexane=1/1-2/1) to give the target compound (140mg) as white solid.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36 and 1.43(9H, 2s), 1.40-1.68(4H, m), 1.85-2.44(9H, m), 3.61(1H, br), 3.83(1H, br), 4.05-4.22(2H, m), 4.35 and 4.40(1H, 2t, J=8.5Hz), 4.34(1H, br).

Example 1-2

(2S)-1-{[(2S,3aS,6R,7aS)-6-Hydroxyoctahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile

To a solution of tert-butyl (2S,3aS,6R,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate obtained in Example 1-1 (140mg) in 1,4-dioxane (2mL), was added dropwise 4N hydrogen chloride in 1,4-dioxane (1.9mL) at 5℃. The mixture was warmed to room temperature and stirred for 3hrs.

The solvent was evaporated. The residue was basified with saturated aqueous sodium hydrogencarbonate and extracted with chloroform. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The organic layer was concentrated, and the solid was washed with isopropylether to give the target compound (57mg) as white solid.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.15-2.37(13H, m), 3.28(1H, m), 3.42-3.66(2H, m), 3.77(1H, m), 3.95(1H, m), 4.79(1H, m).
MS (ES+) m/e : 264.15.

Example 2-1

1-tert-Butyl 2-methyl (2S,3aS,6R,7aR)-6-hydroxyoctahydro-1H-indole-1,2-dicarboxylate

1-Benzyl 2-methyl (2S,3aR,6R,7aR)-6-

hydroxyoctahydro-1H-indole-1,2-dicarboxylate was hydrogenated and then acylated with di-t-buthyl dicarbonate to give the target compound (270mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.1-1.8(6H, m), 1.32(9H, s), 1.76(1H, m), 2.05(1H, m), 2.28(1H, m), 2.95-3.30(2H, m), 3.72(3H, s), 3.74(1H, m), 4.30(1H, m).

Example 2-2

(2S,3aS,6R,7aR)-1-(tert-butoxycarbonyl)-6-hydroxyoctahydro-1H-indole-2-carboxylic acid

To a solution of 1-tert-butyl 2-methyl (2S,3aS,6R,7aR)-6-hydroxyoctahydro-1H-indole-1,2-dicarboxylate (325mg) obtained in Example 2-1 in 1,4-dioxaane (6mL) and water (2mL), was added lithium hydroxide monohydrate (137mg). The mixture was stirred at 50℃ for 12hrs.

The resulting mixture was evaporated in vacuo. To the residue, was added 1N hydrochloric acid (3.5mL), and the mixture was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was triturated with ether to give the target compound (195mg) as a solid.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.0-1.55(5H, m), 1.32(9H, s), 1.71(1H, m), 1.82(1H, m), 2.22(1H, m), 2.75-3.00(2H, m), 3.48(1H, m), 4.10(1H, m), 4.64(1H, m).
MS m/e : 284 (M-1).

Example 2-3

tert-Butyl (2S,3aS,6R,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate

The title compound is prepared from (2S,3aS,6R,7aR)-1-(tert-butoxycarbonyl)-6-hydroxyocta hydro-1H-indole-2-carboxylic acid obtained in Example 2-2 in a similar manner to that of Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35 and 1.45(9H, 2s), 1.20-1.68(11H, m), 1.86(1H, m), 1.98-2.38(3H, m), 3.20(1H, m), 3.59(1H, m), .3.74(1H, m), 4.47(1H, m), 4.84(1H, m).
MS m/e : 364 (M+1).

Example 2-4
(2S)-1-{[(2S,3aS,6R,7aR)-6-hydroxyoctahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride

The title compound is prepared from tert-butyl (2S,3aS,6R,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbo nyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate obtained in Example 2-2 in a similar manner to that of Example 8-4 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.4-2.4(11H, m), 2.56-2.91(2H, m), 3.39(1H, m), 3.42-3.7(2H, m), 4.55(1H, m), 4.84(1H, m).
MS m/e : 264 (free+1).

Example 3-1
(2S,3aS,7aR)-1-(tert-Butoxycarbonyl)octahydro-1H-indo le-2-carboxylic acid

The title compound is prepared from 1-tert-butyl 2-methyl (2S,3aS,7aR)octahydro-1H-indole-1,2-dicarbox ylate in a similar manner to that of Example 2-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.10-1.60(6H, m), 1.48(9H, s), 1.70-1.91(3H, m), 2.31(1H, m), 2.6-3.1(2H, m), 4.27(1H, m).
MS m/e : 268 (M-1).

Example 3-2
tert-Butyl (2S,3aS,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate

The title compound is prepared from (2S,3aS,7aR)-1-(tert-butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid obtained in Example 3-1 in a similar manner to that of Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36 and 1.44(9H, s), 1.30-2.40(12H, m), 3.40-3.70(2H, m), 3.58(2H, m), 3.76(1H, m), 3.98(1H, m), 4.41(1H, m), 4.83(1H, m).
MS m/e : 348 (M+1).

Example 3-3
(2S)-1-[(2S,3aS,7aR)-Octahydro-1H-indol-2-ylcarbonyl]-2-pyrrolidinecarbonitrile hydrochloride

The title compound is prepared from tert-butyl (2S,3aS,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate obtained in Example 3-2 in a similar manner to that of Example 8-4 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.1-2.3(15H, m), 2.6-2.7(2H, m), 3.58(1H, m), 4.44(1H, m), 4.82(1H, m).
MS m/e : 248 (free+1).

Example 4-1

tert-Butyl (2S,3aR,6R,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate

The title compound is prepared from (2S,3aR,6R,7aR)-1-(tert-butoxycarbonyl)-6-hydroxyoctahydro-1H-indole-2-carboxylic acid in a similar manner to that of Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36 and 1.45(9H, 2s), 1.30-2.80(13H, m), 3.58(2H, m), 3.83(1H, m), 3.98(1H, m), 4.36 and 4.41(1H, m), 4.82(1H, m).
MS m/e : 364 (M+1).

Example 4-2
(2S)-1-{[(2S,3aR,6R,7aR)-6-Hydroxyoctahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride

The title compound is prepared from tert-butyl (2S,3aR,6R,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate obtained in Example 4-1 in a similar manner to that of Example 8-4 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.4-2.5(13H, m), 3.39(1H, m), 3.42-3.7(2H, m), 4.75(1H, m), 4.85(1H, m).
MS m/e : 264 (free+1).

Example 5-1
(2S,3aS,7aR)-1-(tert-Butoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-indole-2-carboxylic acid

The title compound is prepared from methyl (2S,3aS,7aR)-1-(tert-butoxycarbonyl)-2,3,3a,4,7,7a-he

xahydro-1H-indole-2-carboxylate in a similar manner to that of Example 2-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.43 and 1.47(9H, s), 1.62(1H, m), 1.75-2.15(3H, m), 2.30(1H, m), 2.44(1H, m), 2.9-3.4(2H, m), 4.34(1H, m), 5.58-5.72(2H, m).
MS m/e : 266 (M-1).

Example 5-2
tert-Butyl (2S,3aS,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate

The title compound is prepared from (2S,3aS,7aR)-1-(tert-butoxycarbonyl)-2,3,3a,4,7,7a-hexahydro-1H-indole-2-carboxylic acid obtained in Example 5-1 in a similar manner to that of Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.37 and 1.45(9H, s), 1.30-2.45(10H, m), 2.94(1H, m), 3.40(1H, m), 3.60(1H, m), 3.77(1H, m), 4.45(1H, m), 4.86(1H, m), 5.60-5.73(2H, m).

Example 5-3
(2S)-1-[(2S,3aS,7aR)-2,3,3a,4,7,7a-Hexahydro-1H-indol-2-ylcarbonyl]-2-pyrrolidinecarbonitrile hydrochloride

The title compound is prepared from tert-butyl (2S,3aS,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate obtained in Example 5-2 in a similar manner to that of Example 8-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.37 and 1.45(9H, s), 1.30-2.45(10H, m), 2.94(1H, m), 3.40(1H, m), 3.60(1H, m),

3.77(1H, m), 4.45(1H, m), 4.86(1H, m), 5.60-5.73(2H, m).

Example 6-1
tert-Butyl (2S,3aR,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate

The title compound is prepared from (2S,3aR,7aS)-1-(tert-butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid in a similar manner to that of Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.44(9H, s), 1.05-2.40(15H, m), 2.84(1H, m), 3.55-3.75(2H, m), 4.43(1H, m), 4.82(1H, m).
MS m/e : 348 (M+1).

Example 6-2
(2S)-1-[(2S,3aR,7aS)-Octahydro-1H-indol-2-ylcarbonyl]-2-pyrrolidinecarbonitrile hydrochloride

The title compound is prepared from tert-butyl (2S,3aR,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate obtained in Example 6-1 in a similar manner to that of Example 8-4 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.05-1.32(2H, m), 1.4-2.35(13H, m), 2.74(1H, m), 3.48-3.63(2H, m), 4.52(1H, m), 4.83(1H, m).
MS m/e : 248 (free+1).

Example 7-1
(2S,3aS,8aR)-1-(tert-Butoxycarbonyl)decahydrocyclohepta[b]pyrrole-2-carboxylic acid

The title compound is prepared from (2S,3aS,8aR)-decahydrocyclohepta[b]pyrrole-2-carboxylic acid in a similar manner to that of Example 14-1 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.1-1.75(9H, s), 1.77(1H, m), 2.06(1H, m), 2.31(1H, m), 2.93(1H, m), 3.55(1H, m), 4.20(1H, m).
MS m/e : 282 (M-1).

Example 7-2
tert-Butyl (2S,3aS,8aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydrocyclohepta[b]pyrrole-1(2H)-carboxylate

The title compound is prepared from (2S,3aS,8aR)-1-(tert-butoxycarbonyl)octahydrocyclohepta[b]pyrrole-1(2H)-carboxylic acid in a similar manner to that of Example 1-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35 and 1.45(9H, s), 1.11-2.40(15H, m), 2.64(1H, m), 2.97(1H, m), 3.45-3.80(3H, m), 4.36(1H, m), 4.84(1H, m).
MS m/e : 362 (M+1).

Example 7-3
(2S)-1-[(2S,3aS,8aR)-Decahydrocyclohepta[b]pyrrol-2-ylcarbonyl]-2-pyrrolidinecarbonitrile hydrochloride

The title compound is prepared from tert-butyl (2S,3aS,8aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydrocyclohepta[b]pyrrole-1(2H)-carboxylate obtained in Example 7-2 in a similar manner to that of Example 8-4 described later.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.15-2.35(17H, m), 2.69(1H, m), 3.33(1H, m), 3.60(1H, m), 4.48(1H, m), 4.83(1H, m).
MS m/e : 262 (free+1).

Example 8-1
(1S,3aS,7aS)-2-(tert-Butoxycarbonyl)octahydro-1H-isoindole-1-carboxylic acid

To a solution of (1S,3aS,7aS)-octahydro-1H-isoindole-1-carboxylic acid (380mg, Tetrahedron Letters 1984, 24(40), p5339) in water/acetone (10/5mL), was added triethylamine (0.78mL) and di-tert-butyl dicarbonate (539mg) with cooling on the ice bath. The reaction mixture was stirred at the room temperature for 2hrs.

The resulting mixture was concentrated in vacuo and acidified with 1N hydrochloric acid to pH3. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and filtered. After removal of the solvent in vacuo, the residue was triturated with diisopropyl ether to give the target compound as a white powder (253mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.03-2.15(20H, m), 2.64(1H, m), 2.82-3.08(1H, m), 3.67-3.90(2H, m).

Example 8-2
tert-Butyl (1S,3aS,7aS)-1-{[(2S)-2-(aminocarbonyl)-1-pyrrolidinyl]carbonyl}octahydro-2H-isoindole-2-carboxylate

1-Hydroxybenzotriazole (44mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (180mg) were added to an ice-cooled suspension of (2S)-2-pyrrolidinecarboxamide (96.6mg) and

(1S,3aS,7aS)-2-(tert-butoxycarbonyl)octahydro-1H-isoindole-1-carboxylic acid (230mg) obtained in Example 8-1 in N,N-dimethylformamide (2mL). Diisopropylethylamine (298μL) was added dropwise and the mixture was stirred at the same temperature for 1hr. The mixture was warmed to room temperature and stirred for 20hrs.

The resulting mixture was partitioned between water and ethyl acetate. The organic layer was washed with 0.5N hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. After removal of the solvent, the target compound was given as a colorless oil.

MS (ES+) m/e : 336 (M+1).

Example 8-3

tert-Butyl (1S,3aS,7aS)-1-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-2H-isoindole-2-carboxylate

To tert-butyl (1S,3aS,7aS)-1-{[(2S)-2-(amino-carbonyl)-1-pyrrolidinyl]carbonyl}octahydro-2H-isoindole-2-carboxylate (312mg) obtained in Example 8-2 in tetrahydrofuran (3mL), were added pyridine (0.21mL) and trifluoroacetic anhydride (0.15mL) with cooling on an ice bath under nitrogen atmosphere. After 10min, the bath was removed and the mixture was stirred for 2hrs at room temperature.

The mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography

(methanol/chloroform=1/30-1/20) to give the target compound as a colorless oil (169mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.03-2.38- (20H, m), 2.98-3.12(1H, m), 3.50-3.90(3H, m), 4.68-4.96(1H, m).

Example 8-4
(2S)-1-[(1S,3aS,7aS)-Octahydro-1H-isoindol-1-ylcarbonyl]-2-pyrrolidinecarbonitrile hydrochloride

To tert-butyl (1S,3aS,7aS)-1-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-2H-isoindole-2-carboxylate (169mg) obtained in Example 8-3 in ethyl acetate (1mL) with cooling on ace bath, was added dropwise 4N hydrogen chloride in ethyl acetate (3mL). The mixture was warmed to room temperature and stirred for 3hrs. The solvent was evaporated and the residue triturated with ethyl acetate to give the target compound as a white solid (4mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.09-1.46(4H, m), 1.70-1.92(5H, m), 1.92-2.11(2H, m), 2.11-2.30(2H, m), 2.37-3.51(1H, m), 3.05-3.28(2H, m), 3.37-3.52(1H, m), 3.56-3.60(1H, m), 3.78-3.88(1H, m), 4.36-4.47(1H, m), 4.47-5.57(1H, m). MS (ES+) m/e : 248.40 (M+1).

Example 9-1
1-Benzyl 2-methyl (2S,3aS,7aS)-6-(dimethylamino)-octahydro-1H-indole-1,2-dicarboxylate

To a mixture of 1-benzyl 2-methyl (2S,3aS,7aS)-6-oxooctahydro-1H-indole-1,2-dicarboxylate (1.0g, 3.02mmol), 2M dimethylamine in tetrahydrofuran (1.66mL) and acetic acid (181mg) in tetrahydrofuran, was added sodium triacetoxyborohydride (943mg, 4.23mmol) at

room temperature. The mixture was stirred at same temperature for 6hrs.

To the reaction mixture, was added saturated aqueous sodium bicarbonate solution. The mixture was stirred for 15min, and evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (chloroform-methanol=50-1 to 20-1) to give the target compound (538mg, 49%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35-1.80(4H, m), 1.90-2.50(12H, m), 3.48-3.86(3H, m), 4.05-4.39(2H, m), 4.94-5.20(2H, m), 7.18-7.40(5H, m).
MS (ES+) m/z : 361.

Example 9-2
Methyl (2S,3aS,7aS)-6-(dimethylamino)octahydro-1H-indole-2-carboxylate

A mixture of 1-benzyl 2-methyl (2S,3aS,7aS)-6-(dimethylamino)octahydro-1H-indole-1,2-dicarboxylate obtained in Example 9-1 (536mg, 1.49mmol) and 10% palladium on carbon (120mg) in a mixture of methanol (10mL) and dioxane (5mL) was stirred at room temperature under hydrogen for 30min.

The reaction mixture was filtered through Celite and evaporated in vacuo to give the target compound (335mg, 100%) as an oil.

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.30-2.50(9H, m), 2.75(6H, s), 3.37-3.60(2H, m), 3.74(3H, s), 3.74-3.95(1H, m).
MS (ES+) m/z : 227.

Example 9-3

(2S,3aS,7aS)-1-(tert-Butoxycarbonyl)-6-(dimethylamino)octahydro-1H-indole-2-carboxylic acid

To a solution of methyl (2S,3aS,7aS)-6-(dimethylamino)octahydro-1H-indole-2-carboxylate (335mg, 1.48mmol) obtained in Example 9-2 in 1,4-dioxane (4mL), was added 1N sodium hydroxide solution (1.78mL) at room temperature. The mixture was stirred at same temperature for 4hrs. After cooling at 0℃, di-tert-butyl dicarbonate (388mg, 1.78mmol) was added to the reaction mixture, and the mixture was stirred at same temperature for 18hrs.

The mixture was evaporated in vacuo and the residue was dissolved in water. The solution was washed with ether, adjusted to pH4 with 1mol/L hydrochloric acid, and extracted with a mixture of chloroform and methanol (5:1). The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give the target compound (391mg, 85%) as a powder.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.37(9H, s), 1.58-1.85(3H, m), 1.85-2.15(3H, m), 2.15-2.35(2H, m), 2.68(6H, s), 3.39-3.55(1H, m), 3.92-4.05(1H, m), 4.05-4.16(1H, m), 4.31-4.44(1H, m).
MS (ES+) m/z : 313.

Example 9-4

tert-Butyl (2S,3aS,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-(dimethylamino)octahydro-1H-indole-1-carboxylate

To a solution of (2S,3aS,7aS)-1-(tert-butoxycarbonyl)-6-(dimethylamino)octahydro-1H-indole-2-carboxylic acid obtained in Example 9-3 (364mg,

1.17mmol) in dimethylformamide (3mL), were added (2S)-pyrrolidine-2-carbonitrile hydrochloride (201mg, 1.51mmol), 1-Hydroxybenzotriazole (220mg, 1.63mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI, 235mg, 1.51mmol) under nitrogen at 0℃. The mixture was stirred at room temperature for 18hrs.

The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel chromatography (chloroform-methanol=20-1) to give the target compound (108mg, 24%) as a powder.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.30-1.63(12H, m), 1.63-1.84(2H, m), 1.84-2.50(15H, m), 3.54-3.66(1H, m), 3.75-3.90(1H, m), 4.00-4.16(1H, m), 4.37(1H, t, J=8Hz), 4.80-4.90(1H, m).
MS (ES+) m/z : 391.

Example 9-5
(2S)-1-{[(2S,3aS,7aS)-6-(Dimethylamino)octahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile bis(trifluoroacetate)

To a solution of tert-butyl (2S,3aS,7aS)-2-{[(2S)-2-cyanopyrrolidin-1-yl]carbonyl}-6-(dimethylamino)octahydro-1H-indole-1-carboxylate (60mg, 0.154mmol) obtained in Example 9-4 in dichloromethane (2mL), was added trifluoroacetic acid (0.5mL) at room temperature. The mixture was allowed to stand for 30min. The solvent was evaporated in vacuo to give the target compound (75mg, 94%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.24-1.69(2H, m), 1.84-2.04(2H,

m), 2.04-2.40(6H, m), 2.40-2.60(1H, m), 2.60-2.96(8H, m), 3.48-3.80(3H, m), 4.25(1H, br peak), 4.70-4.85(2H, m).
MS (ES+) m/z : 291.

Example 10-1
tert-Butyl (2S,3aS,4S,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-4-hydroxyoctahydro-1H-indole-1-carboxylate

The title compound is prepared from tert-butyl (2S,3aS,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate in a similar manner to that of Example 13-2 described later by HPLC purification.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.21-1.46(9H, m), 1.46-2.41(1H, m), 3.52-3.69(2H, m), 3.69-3.90(1H, m), 3.90-4.20(3H, m), 4.28-4.45(1H, m), 4.76-4.90(1H, m).
MS (ES+) m/z : 364.

Example 10-2
(2S)-1-{[(2S,3aS,4S,7aS)-4-Hydroxyoctahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile hydrochloride

The title compound is prepared from tert-Butyl (2S,3aS,4S,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-4-hydroxyoctahydro-1H-indole-1-carboxylate obtained in Example 10-1 in a similar manner to that of Example 8-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.70-2.40(13H, m), 3.65-3.70(2H, m), 4.40-4.70(2H, m), 4.78-4.90(1H, m).
MS (ES+) m/z : 264.

Example 11-1

1-Benzyl 2-methyl (2S,3aS,6R,7aS)-6-azidooctahydro-1H-indole-1,2-dicarboxylate

To a solution of 1-benzyl 2-methyl (2S,3aS,6S,7aS)-6-hydroxyoctahydro-1H-indole-1,2-dicarboxylate (939mg, 2.82mmol) in dichloromethane (10mL), were added triethylamine (570mg, 5.63mmol) and mathanesulfonyl chloride (335mg, 3.1mmol) at 0℃ under nitrogen. The mixture was stirred at same temperature for 1hr.

The residue was partitioned between diluted hydrochloric acid and chloroform. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was dissolved in dimethylformamide (10mL). To the solution was added sodium azide (201mg, 3.1mmol) at room temperature, and the mixture was stirred at 100℃ for 4hrs. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with diluted hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate=1-1) to give the target compound (800mg, 43.1%) as an oil.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.52-1.68(2H, m), 1.68-1.84(1H, m), 1.84-2.08(3H, m), 2.15-2.25(2H, m), 2.25-2.44(2H, m), 2.52-2.80(3H, m), 3.91-3.98(1H, m), 4.04-4.24(1H, m), 4.25-4.40(1H, m), 5.00-5.20(2H, m), 7.25-7.40(5H, m).
MS (ES+) m/z : 359.

Example 11-2

Methyl (2S,3aS,6R,7aS)-6-aminooctahydro-1H-indole-2-

carboxylate

The title compound is prepared from 1-benzyl 2-methyl (2S,3aS,6R,7aS)-6-azidooctahydro-1H-indole-1,2-dicarboxylate obtained in Example 11-1 in a similar manner to that of Example 9-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.04-1.32(2H, m), 1.32-2.00(5H, m), 2.10-2.20(1H, m), 2.20-2.32(1H, m), 2.96-3.12(1H, m), 3.24-3.44(1H, m), 3.68-3.88(4H, m).
MS (ES+) m/z : 199.

Example 11-3
(2S,3aS,6R,7aS)-1-(tert-Butoxycarbonyl)-6-[(tert-butoxycarbonyl)amino]octahydro-1H-indole-2-carboxylic acid

The title compound is prepared from methyl (2S,3aS,6R,7aS)-6-aminooctahydro-1H-indole-2-carboxylate obtained in Example 11-2 in a similar manner to that of Example 9-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36-1.52(18H, m), 1.52-1.92(4H, m), 1.92-2.85(5H, m), 3.80(1H, br peak), 3.72-4.04(1H, m), 4.24-4.36(1H, m).
MS (ES-) m/z : 383.

Example 11-4
tert-Butyl (2S,3aS,6R,7aS)-6-[(tert-butoxycarbonyl)-amino]-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate

The title compound is prepared from (2S,3aS,6R,7aS)-1-(tert-Butoxycarbonyl)-6-[(tert-butoxycarbonyl)amino]octahydro-1H-indole-2-carboxylic

acid obtained in Example 11-3 in a similar manner to that of Example 9-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.32-1.48(12H, m), 1.56-1.68(11H, m), 1.68-2.40(9H, m), 3.52-3.64(1H, m), 3.76-4.00(4H, m), 4.28-4.60(2H, m), 4.68-4.90(1H, m).
MS (ES+) m/z : 463.

Example 11-5
(2S)-1-{[(2S,3aS,6R,7aS)-6-Aminooctahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile bis(trifluoroacetate)

The title compound is prepared from tert-Butyl (2S,3aS,6R,7aS)-6-[(tert-butoxycarbonyl)-amino]-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate obtained in Example 11-4 in a similar manner to that of Example 9-5.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.16-1.56(6H, m), 1.56-2.40(9H, m), 3.48-3.90(2H, m), 4.50-4.70(1H, m), 4.70-4.90(1H, m).

Example 12-1
1-Benzyl 2-methyl (2S,3aS,7aS)-6-(methylamino)-octahydro-1H-indole-1,2-dicarboxylate

The title compound is prepared from 1-benzyl 2-methyl (2S,3aS,7aS)-6-oxooctahydro-1H-indole-1,2-dicarboxylate in a similar manner to that of Example 9-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.30-1.85(8H, m), 1.90-2.51(4H, m), 3.50,3.80(3H, m), 3.91-4.16(1H, m), 4.25-4.40(1H, m), 4.95-5.21(2H, m), 7.25-7.40(5H, m).
MS (ES+) m/z : 347.

Example 12-2

Methyl (2S,3aS,7aS)-6-(methylamino)octahydro-1H-indole-2-carboxylate

The title compound is prepared from 1-benzyl 2-methyl (2S,3aS,7aS)-6-(methylamino)-octahydro-1H-indole-1,2-dicarboxylate obtained in Example 12-1 in a similar manner to that of Example 9-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.20-2.44(8H, m), 2.63(3H, s), 2.88-3.04(1H, m), 3.32-3.40(1H, m), 3.40-3.48(1H, m), 3.75(3H, s), 3.80(1H, dd, J=11,5Hz).
MS (ES+) m/z : 213.

Example 12-3

(2S,3aS,7aS)-1-(tert-Butoxycarbonyl)-6-[(tert-butoxycarbonyl)(methyl)amino]octahydro-1H-indole-2-carboxylic acid

The title compound is prepared from methyl (2S,3aS,7aS)-6-(methylamino)octahydro-1H-indole-2-carboxylate obtained in Example 12-2 in a similar manner to that of Example 9-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.32-1.52(20H, m), 1.60-1.90(2H, m), 2.00-2.48(4H, m), 2.64-2.75(4H, m), 3.88-4.08(2H, m), 4.25-4.40(1H, m).
MS (ES-) m/z : 397.

Example 12-4

tert-Butyl (2S,3aS,7aS)-6-[(tert-butoxycarbonyl)-(methyl)amino]-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate

The title compound is prepared from (2S,3aS,7aS)-1-(tert-butoxycarbonyl)-6-[(tert-butoxycarbonyl)(methyl)amino]octahydro-1H-indole-2-carboxylic acid obtained in Example 12-3 in a similar manner to that of Example 9-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.32-1.52(12H, m), 1.52-1.72(11H, m), 1.72-2.40(9H, m), 2.68-2.84(3H, m), 3.60(1H, br peak), 3.80-4.48(6H, m), 4.70-4.88(1H, m).
MS (ES+) m/z : 477.

Example 12-5
(2S)-1-{[(2S,3aS,7aS)-6-(Methylamino)octahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile bis(trifluoroacetate)

The title compound is prepared from tert-butyl (2S,3aS,7aS)-6-[(tert-butoxycarbonyl)-(methyl)amino]-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate obtained in Example 12-4 in a similar manner to that of Example 9-5.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.08-1.60(6H, m), 1.60-2.40(9H, m), 2.48-2.60(3H, m), 3.20-4.00(3H, m), 4.68-4.88(1H, m).
MS (ES+) m/z : 277.

Example 13-1
tert-Butyl (2S,3aS,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate

To a suspension of (2S)-2-pyrrolidinecarbonitrile hydrochloride (383mg, 2.89mmol), (2S,3aS,7aS)-1-(tert-butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid

(778mg, 2.89mmol), 1-hydroxybenzotriazole hydrate (487mg, 3.18mmol) in dimethylformamide (20mL), were added Water Soluble Carbodiimide (609mg, 3.18mmol) and triethylamine (0.81mL, 5.78mmol) in water bath. The mixture was stirred for 18hrs at room temperature.

To this mixture, was added a solution of saturated aqueous sodium bicarbonate solution and water. The white precipitate was dissolved in ethyl acetate. The layers were separated, and the organic layer washed with saturated aqueous sodium bicarbonate solution and brine. The organic fraction was dried over magnesium sulfate and filtered to give crude product. This crude product was purified by flash chromatography on silica gel 60, eluting with a mixture of ethyl acetate and hexane (2 : 1). The relevant fractions were collected to give the target (700mg, 69.7%) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.04-1.23(1H, m), 1.36 and 1.43(9H, 2s), 1.26-2.40(15H, m), 3.55-3.90(3H, m), 4.27-4.52(1H, m), 4.80-4.90(1H, m).
MS (ES+) m/z : 348.18.

Example 13-2
tert-Butyl (2S,3aS,6R,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate

(1) Fermentation of *Nonomuraea reseoviolacea* JCM-3145

A stock culture of *Nonomuraea reseoviolacea* JCM-3145 is prepared and maintained on agar slant. A loopful of the slant culture was inoculated into a seed medium consisting of sucrose 0.5%, glucose 0.5%, oatmeal 0.5%, yeast extract 0.2%, peptone 0.5%, peanut powder 0.5%, "HUMAS" (Aiaisi kabushikikaisha, Osaka, Japan) as humic acid 0.01%, polyoxyethylene sorbitan monooleate 0.1% and

$CaCO_3$ 0.2% (pH 7.0 adjusted with 6N NaOH). The inoculated vegetative medium (60mL) was shaken on a rotary shaker (220rpm, 5.1 cm throw) in a 225mL Erlenmeyer flask at 30℃ for about 72hrs. 8mL of the seed culture was transferred to 160mL of the same sterile seed medium in the 500-ml Erlenmeyer flasks. The flasks were shaken on a rotary shaker (220rpm, 5.1 cm throw) at 30℃ for about 72hrs, and 480mL (three flasks) of the second culture was inoculated to sterile production medium (20L) consisting of corn flour 1.0%, MS#3600 (modified starch) 6.0%, pharmamedia 1.2%, dried yeast 0.8%, KH_2PO_4 0.3% and $MgSO_4 \cdot 7H_2O$ 0.3% and $FeSO_4 \cdot 7H_2O$ 0.02% (pH 6.5 adjusted with 6N NaOH). The inoculated production medium was allowed to ferment in a 30L jar fermentor at a temperature of 30℃ for about 72hrs. The fermentation medium was stirred with conventional agitators at 200rpm and aerated at 20L per minute. The cultured broth was used to obtain the target compound.

(2) Reaction condition

To a solution of the tert-butyl (2S,3aS,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate obtained in Example 13-1 (9g) in methanol (0.4L), was added 20L of cultured broth of *Nonomuraea reseoviolacea* JCM-3145. The reaction was carried out at 30℃ with stirring for 70hrs. Increase of the target compound was monitored by analytical HPLC indicated below.

Analytical HPLC condition:

Column : Mightysil RP-18 GP 250-4.6
(250mm L.X 4.6 I.D.,Kanto Chemical Co.,Inc)

Eluent : 35% aqueous acetonitrile, 0.5% $NaH_2PO_4 \cdot H_2O$

Flow rate : 1ml/min.

Detection : UV at 210nm

Retention time or the target compound : 6.9min.

As the result of HPLC, some compounds having different position or conformation of hydroxy group were obtained. From 18g of the tert-butyl (2S,3aS,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl }octahydro-1H-indole-1-carboxylate obtained in Example 13-1, 6.4g of the target compound was formed in the reaction mixture.

(3) Isolation of the target compound

The reaction mixture (40L) was extracted with an equal volume of acetone by stirring for 2hrs at room temperature. The mixture was filtered with an aid of diatomaceous earth. The filtrate was diluted with an equal of water and passed through a column (4L) of DIAION HP-20 (Mitsubishi Chemical Co., Ltd.) packed with 25% aqueous acetone. The column was washed with water (15L) and then eluted with 30% aqueous acetonitrile containing 0.5% $NaH_2PO_4 \cdot H_2O$ (41L). The eluate was diluted with equal volume of water and passed through a column (18L) of Daisogel SP-120-ODS-B (15/30mm, DAISO Co., Ltd., Japan) packed with 15% aqueous acetonitrile. The column was washed with water (80L) and eluted with 25% aqueous acetonitrile. Active fraction (133-138L) was diluted with equal volume of water and passes through a column (2L) of Daisogel SP-120-ODS-B (15/30mm, DAISO Co., Ltd., Japan) packed with 12.5% aqueous acetonitrile. The column was washed with water (2L) and eluted with 25% aqueous acetonitrile. Active fraction (5.15-6.54L) was diluted with equal volume of water and passed through a column (2L) of Daisogel SP-120-ODS-B (15/30mm, DAISO Co., Ltd., Japan) packed with 12.5% aqueous acetonitrile. The column was washed with water (5L) and then eluted with methanol (1.2L). The eluate was concentrated in vacuo to give 1.1g of the target

compound as a white powder.

The target compound can be used as the material compound of Example 1-2 to synthesize (2S)-1-{[(2S,3aS,6R,7aS)-6-hydroxyoctahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile.

Example 14-1
(2S,3aR,7aR)-1-(tert-Butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid

To a solution of (2S,3aR,7aR)-octahydro-1H-indole-2-carboxylic acid (450mg) in 1,4-dioxane (11mL) and water (2mL), were added 0.5N sodium hydroxide solution (5.85mL) and di-tert-butyl dicarbonate (609mg). The mixture was stirred at 20℃ for 12hrs.

The resulting mixture was acidified with citric acid (pH ca.4), and partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residual solid was washed with hexane to give the title compound as a white powder (320mg).

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.03-1.44(4H, m), 1.32 and 1.38(9H, 2s), 1.47-1.73(4H, m), 1.86-2.00(1H, m), 2.20-2.40(2H, m), 3.59-3.74(1H, m), 4.04-4.10(1H, m), 12.44(1H, br s).
MS(ES-) m/z : 268(M-1).

Example 14-2
tert-Butyl (2S,3aR,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate

To a mixture of (2S,3aR,7aR)-1-(tert-butoxycarbonyl)octahydro-1H-indole-2-carboxylic acid

obtained in Example 14-1 (282mg), (2S)-2-pyrrolidinecarbonitrile hydrochloride (153mg), and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (418mg) in N,N-dimethylformamide (5.0mL), was added dropwise N,N-diisopropylethylamine (0.57mL) at 5℃. The mixture was stirred for 1hr.

The resulting mixture was poured into 5% aqueous potassium hydrogen sulfate. The mixture was extracted with ethyl acetate and washed with saturated aqueous sodium hydrogencarbonate, water, and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluent: hexane / ethyl acetate = 1/1). After removal of the solvent, the residual oil was triturated with hexane to give the title compound as white crystals (198mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.03-1.52(4H, m), 1.35 and 1.44(9H, 2s), 1.57-1.74(4H, m), 2.05-2.34(6H, m), 2.60-2.78(1H, m), 3.50-4.00(3H, m), 4.32-4.42(1H, m), 4.80-4.87(1H, m).
MS(ES+) m/z : 348(M+1).

Example 14-3
(2S)-1-[(2S,3aR,7aR)-Octahydro-1H-indol-2-ylcarbonyl]-2-pyrrolidinecarbonitrile trifluoroacetate

tert-Butyl (2S,3aR,7aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate obtained in Example 14-2 (150mg) was dissolved in trifluoroacetic acid (1.5mL), and the mixture was stirred for 1hr at 20℃. The resulting mixture was evaporated in vacuo. The residual oil was triturated with ether to give the title compound as white crystals (100mg).

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.24-1.52(4H, m), 1.53-1.80(4H, m), 1.85-2.47(7H, m), 3.48-3.57(1H, m), 3.58-3.71(2H, m), 4.53 and 4.65(1H, 2m), 4.85 and 5.03(1H, 2m), 9.08(2H, br).
MS(ES+) m/z : 248(free+1).

Example 15-1
tert-Butyl (2S,3aR,6aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate

The title compound is prepared from (2S,3aR,6aR)-1-(tert-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid and (2S)-2-pyrrolidinecarbonitrile hydrochloride in a similar manner to that of Example 14-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.37 and 1.45(9H, 2s), 1.40-1.70(4H, m), 1.71-2.04(4H, m), 2.05-2.36(4H, m), 2.84-3.00(1H, m), 3.47-3.73(2H, m), 4.26-4.56(2H, m), 4.79-4.85(1H, m).
MS(ES+) m/z : 334(M+1).

Example 15-2
(2S)-1-[(2S,3aR,6aR)-Octahydrocyclopenta[b]pyrrol-2-ylcarbonyl]-2-pyrrolidinecarbonitrile trifluoroacetate

The title compound is prepared from tert-butyl (2S,3aR,6aR)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate obtained in Example 15-1 in a similar manner to that of Example 14-3.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.42-1.57(2H, m),

1.63-2.34(10H, m), 2.78(1H, m), 3.51-3.61(1H, m), 3.67-3.76(1H, m), 4.14(1H, m), 4.56(1H, m), 4.83(1H, m), 9.02(1H, br), 9.27(1H, br).
MS(ES+) m/z : 234(free+1).

Example 16-1
Methyl (2S)-2-amino-3-hydroxypropanoate hydrochloride

To a solution of serine (25g) in methanol (280mL), was added thionyl chloride(19.1mL) at room temperature. This solution was heated at reflux for 3hrs. The resulting mixture was cooled to room temperature, and the solvent was removed in vacuo to give the target compound as a white powder (36.7g).

^{1}H-NMR (in $CDCl_3$) : δ 3.74(3H, s), 3.80-3.86(2H, m), 4.07-4.14(1H, m), 5.47-5.86(1H, m), 8.61(3H, brs).

Example 16-2
Methyl N-acethyl-L-serinate

To a solution of methyl (2S)-2-amino-3-hydroxypropanoate hydrochloride obtained in Example 16-1, acetic acid and triethyl amine in methylene chloride with cooling on the ice bath, was added N,N'-dicyclohexylcarbodiimede. The reaction mixture was warmed to room temperature and stirred for 5hrs.

After removal of the solvent, the residue was washed with tetrahydrofuran and the filtration was evaporated in vacuo. The residue was purified with silica gel chromatography (methanol/ethyl acetate = 1/12 to 1/9) to give the target compound as a colorless oil (24.5g).

^{1}H-NMR (in $CDCl_3$) : δ 2.08(3H, s), 2.45-2.54(1H, m),

3.81(3H, s), 3.89-4.04(2H, m), 4.63-4.73(1H, m), 6.38-6.53(1H, m).
MS (ES+) m/z : 162.16 (M+1).

Example 16-3
Methyl N-acethyl-3-chloro-L-alaninate

To a solution of methyl N-acethyl-L-serinate obtained in Example 16-2 (24.5g) in tetrahydrofuran (200mL) with cooling on an ice bath, was added thionyl chloride (23mL). The reaction mixture was stirred at room temperature for 1hr and quenched by adding water.

The aqueous layer was extracted with ethyl acetate and combined organic layer was washed with brine, dried over magnesium sulfate, and filtered. After removal of the solvent in vacuo, the residue was triturated with diethyl ether to give the target compound as a white powder (10.5g).

^{1}H-NMR (in $CDCl_3$) : δ 2.09(3H, s), 3.83(3H, s), 3.85-4.04(2H, m), 4.95-5.07(1H, m), 6.29-6.46(1H, m).

Example 16-4
Methyl N-acethyl-3-(2-oxocyclopentyl)-L-alaninate

A solution of 1-cyclopent-1-en-1-ylpyrrolidine in dimethylformamide (5mL) was added to a solution of methyl N-acethyl-3-chloro-L-alaninate obtained in Example 16-3 and triethylamine in dimethylformamide (50mL) dropwise with cooling on an ice bath. The reaction mixture was warmed to room temperature and stirred at room temperature for 2hrs.

The reaction mixture was concentrated in vacuo and quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over

magnesium sulfate, and filtered. After removal of the solvent in vacuo, the residue was purified with silica gel chromatography (n-hexane/ethyl acetate = 1/2 to 1/3) to give the target compound as a yellow oil (12.9g).

^{1}H-NMR (in $CDCl_3$) : δ 1.48-2.46(12H, m), 3.74(1.65H, s), 3.75(1.35H, s), 4.55-4.70(1H, m), 6.42-6.50(0.55H, m), 6.67-6.77(0.45H, m).
MS (ES+) m/z : 228.31 (M+1).

Example 16-5
(2S)-2,3,3a,4,5,6,-Hexahydrocyclopenta[b]pyrrole-2-carboxylic acid hydrochloride

Methyl N-acethyl-3-(2-oxocyclopentyl)-L-alaninate obtained in Example 16-4 was dissolved in 6% hydrochloric acid (160mL), and the mixture was heated at reflux for 1hr. After removal of the solvent in vacuo, the crude product of the target compound was given as an yellow oil (14g).

MS (ES+) m/z : 154.15 (M+1).

Example 16-6
(2S, 3aS, 6aS)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid hydrochloride

The crude product of (2S)-2,3,3a,4,5,6,-hexahydrocyclopenta[b]pyrrole-2-carboxylic acid hydrochloride obtained in Example 16-5 (14g) was dissolved in acetic acid (200mL) and 10% Pd/C (3.6g) was added. The mixture was hydrogenated under H_2 (4atm) at room temperature for 6hrs.

The catalyst was filtered through a celite pad and washed with acetic acid. The filtrate was concentrated

in vacuo, and the residue was triturated with chloroform to give the target compound as a white powder (1.1g).

^{1}H-NMR (in $CDCl_3$) : δ 1.33-2.79(7H, m), 2.34-2.51(1H, m), 2.69-2.90(1H, m), 3.85-4.07(1H, m), 4.15-4.41(1H, m), 8.48-8.93(1H, m), 10.2-10.8(2H, m).
MS (ES+) m/z : 156.14 (M+1).

Example 16-7
(2S, 3aS, 6aS)-1-(tert-Butoxylcarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid

A solution of di-tert-butyl dicarbonate(1.5 g) in dioxane(8mL) was added to the solution of (2S, 3aS, 6aS)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid hydrochloride (1.0g) obtained in Example 16-6 in dioxane/1N NaOH (8/16mL) with cooling on the ice bath. The reaction mixture was stirred at the room temperature for 2hrs. The resulting mixture was concentrated in vacuo, the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and filtered. After removal of the solvent in vacuo, the residue was triturated with diethyl ether to give the target compound as a white powder (462mg).

^{1}H-NMR (in $CDCl_3$) : δ 1.32-1.94(15H, m), 2.14-2.44(2H, m), 2.59-2.75(1H, m), 4.12-4.27(1H, m), 4.37-4.49(1H, m).
MS (ES+) m/z : 256.39 (M+1), (ES-) m/z : 254.27 (M-1).

Example 16-8
tert-Butyl (2S,3aS,6aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate

The title compound is prepared from (2S, 3aS,

6aS)-1-(tert-butoxylcarbonyl)octahydro-cyclopenta[b]pyrrole-2-carboxylic acid obtained in Example 16-7 in a similar manner to that of Example 1-1.

^{1}H-NMR (in $CDCl_3$) : δ 1.29-2.48(21H, m), 2.61-2.78(1H, m), 3.46-3.76(2H, m), 4.11-4.29(1H, m), 4.32-4.51(1H, m), 4.77-4.88(1H, m).
MS (ES+) m/z : 334.47 (M+1).

Example 16-9
(2S)-1-[(2S,3aS,6aS)-Octahydrocyclopenta[b]pyrrol-2-ylcarbonyl]-2-pyrrolidinecarbonitrile

The title compound is prepared from tert-butyl (2S,3aS,6aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate obtained in Example 16-8 in a similar manner to that of Example 1-2.

^{1}H-NMR (in $CDCl_3$) : δ 1.22-1.82(9H, m), 2.05-2.42(4H, m), 2.53-2.69(1H, m), 3.49-3.69(4H, m), 4.78-4.93(1H, m).
MS (ES+) m/z : 234.35 (M+1).

Example 17-1
tert-Butyl (2S,3aS,6S,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate

The title compound is prepared from tert-butyl (2S,3aS,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate in a similar manner to that of Example 13-2 by HPLC purification.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.31-1.50(9H, m), 1.50-1.86(7H, m), 2.00-2.12(1H, m), 2.12-2.52(5H, m), 3.45-3.65(2H, m),

3.75-4.05(2H, m), 4.31-4.45(1H, m), 4.79-4.90(1H, m).
MS (ES+) m/z : 364.

Example 17-2

The title compound is prepared from tert-butyl (2S,3aS,6S,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-6-hydroxyoctahydro-1H-indole-1-carboxylate obtained in Example 17-1 in a similar manner to that of Example 8-4.

^{1}H-NMR (300MHz, DMSO-d_6) : δ 1.29-2.40(13H, m), 3.48-3.74(3H, m), 3.74-3.95(1H, m), 4.34-4.60(1H, m), 4.76-4.90(1H, m).

Example 18-1
tert-Butyl (2S,3aR,5S,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-5-hydroxyoctahydro-1H-indole-1-carboxylate

The title compound is prepared from tert-butyl (2S,3aR,5S,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}octahydro-1H-indole-1-carboxylate in a similar manner to that of Example 13-2.

Example 18-2
(2S)-1-{[(2S,3aR,5S,7aS)-5-Hydroxyoctahydro-1H-indol-2-yl]carbonyl}-2-pyrrolidinecarbonitrile

The title compound is prepared from tert-butyl (2S,3aR,5S,7aS)-2-{[(2S)-2-cyano-1-pyrrolidinyl]carbonyl}-5-hydroxyoctahydro-1H-indole-1-carboxylate obtained in Example 18-1 in a similar manner to that of Example 1-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.15-2.50(13H, m), 3.14(1H, m), 3.55(2H, m), 3.84(1H, m), 3.96(1H, m), 4.79(1H, m).
MS (ES+) m/z : 264 (M+1).

In order to illustrate the usefulness of the object Compound (I), the pharmacological test is carried out as shown in the following.

[A] Inhibition test of human plasma DPP-IV :

(i) Material and Method :

The effect of test compounds on DPP-IV activity in human plasma was evaluated with a modified version of the assay described by Hughes et al (Biochemistry, 38, pp11597-11603(1999)).

Briefly, 20μL of human plasma were mixed with 20 μL of 80mM $MgCl_2$ in assay buffer (25mM HEPES, 140mM NaCl, 1% RIA-grade BSA, pH7.8), and were incubated in a room temperature for 60min. Then the reaction was initiated by the addition of both 20μL of test compounds and 20 μL of 0.2mM substrate (H-glycine-proline-AMC; AMC is 7-amino-4-methylcoumarine), they were dissolved in the assay buffer.

After 20min incubation in a room temperature (kept in the dark), fluorescence was measured (Excitation 380nm, Emission 460nm). A fluorescence-concentration curve of free AMC was obtained using AMC solution in the assay buffer with appropriate concentration. Plasma DPP-IV activities, with or without the test compounds, were expressed as the amount of product per minute per mL. The potency of the test compounds as DPP-IV inhibitor was expressed as IC_{50}.

(ii) Results :

The following IC_{50} values were obtained.

Table 1

Compound	IC_{50} value for human plasma DPP-IV (nM)
Example 1-2	6.8
LAF 237	24

It appeared, from the above-mentioned Inhibition test, that the compound (I) and (1) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against DPP-IV.

Therefore, the compound (I) and (1) or pharmaceutically acceptable salts thereof are useful for treating or preventing disease mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

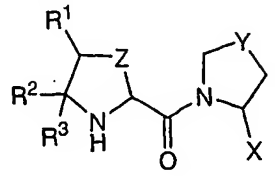
Further, the compound (I) and (1) or pharmaceutically acceptable salts thereof are useful for treating or preventing autoimmune disease, arthritis, rejection of transplanted organs, systemic lupus erythematosus (SLE), acquired immunodeficiency syndrome (AIDS), hypertension, atherosclerosis, gallbladder disease, cancer, intestinal disease and dwarfism.

The patents, patent applications and publications cited herein are incorporated by reference.

This application is based on Australian Provisional Application No.2003902946 filed on June 12, 2003, the contents of which are hereby incorporated by references.

C L A I M S

1. A compound of the formula (I) or pharmaceutically acceptable salt thereof.



(I)

[wherein

X is cyano or H;

Y is CH_2, O, S, SO or SO_2;

Z is (lower)alkylene (which may be substituted with R^4), O, S, SO or SO_2;

R^1 and R^2 each is independently H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; R^3 is (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; and R^4 is hydroxy or hydroxy[(lower)alkyl]; or

R^1 and R^2 are linked together to form (lower)alkylene or (lower)alkenylene; R^3 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; and R^4 is hydroxy or hydroxy[(lower)alkyl]; or

R^1 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; R^2 and R^3 are linked together to form (lower)alkylene or (lower)alkenylene; and R^4 is hydroxy or hydroxy[(lower)alkyl]; or

R^1 and R^4 are linked together to form (lower)alkylene or (lower)alkenylene; R^2 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl]; and R^3 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl];

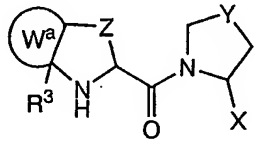
the (lower)alkylene or (lower)alkenylene formed by R^1 and R^2, R^2 and R^3, or R^1 and R^4 may be substituted; and

the substituent(s) on the (lower)alkylene or (lower)alkenylene is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy,

hydroxy[(lower)alkyl], oxo, [(lower)alkane]sulfonylamide and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl, aryl (which may be substituted) or heteroaryl (which may be substituted));

the substituent(s) on the aryl or heteroaryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy and hydroxy[(lower)alkyl].]

2. A compound of the formula (Ia) or pharmaceutically acceptable salt thereof.



(Ia)

[wherein

X is cyano or H;

Y is CH_2, O, S, SO or SO_2;

Z is (lower)alkylene (which may be substituted with R^4), O, S, SO or SO_2;

W^a is cycloalkyl or cycloalkenyl which may be substituted;

R^3 is H, (lower)alkyl, hydroxy or hydroxy[(lower)alkyl];

R^4 is hydroxy or hydroxy[(lower)alkyl];

the substituent(s) on the cycloalkyl or (lower)alkenyl is(are) selected form the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano, nitro, amino, hydroxy, hydroxy[(lower)alkyl] oxo, [(lower)alkane]sulfonylamide and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl, aryl (which may be substituted) or heteroaryl (which may be substituted));

the substituent(s) on the aryl or heteroaryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, carboxy, sulfonic acid, halogen, cyano,

nitro, amino, hydroxy and hydroxy[(lower)alkyl].]

3. The compound of Claim 2, wherein X is cyano.

4. The compound of Claim 2 or 3, wherein Y is CH_2.

5. The compound of any one of Claim 2 to 4, wherein Z is (C1-C2)alkylene.

6. The compound of any one of Claim 2 to 4, wherein Z is methylene.

7. The compound of any one of Claim 2 to 6, wherein W^a is cycloalkyl which may be substituted.

8. The compound of any one of Claim 2 to 6, wherein W^a is cyclohexyl which may be substituted.

9. The compound of any one of Claim 2 to 8, wherein R^3 is H.

10. The compound of any one of Claim 2 to 9, wherein the substituent(s) on the cycloalkyl or (lower)alkenyl is(are) selected form the group consisting of amino, hydroxy, hydroxy[(lower)alkyl] and $-NR^5R^6$ (R^5 is H or (lower)alkyl; R^6 is (lower)alkyl.

11. The compound of any one of Claim 2 to 9, wherein the substituent(s) on the cycloalkyl or (lower)alkenyl is(are) hydroxy.

12. A method for producing the compound of Claim 11, comprising bio-conversion step, wherein hydroxy group is introduced on the cycloalkyl or (lower)alkenyl by actinomycetes.

13. The method of Claim 12, wherein the actinomycetes is *Nonomuraea reseoviolacea* JCM-3145

14. The method of Claim 12 or 13, wherein the introduction of the hydroxy group is stereoselective.

15. A medicament comprising a compound of any one of Claim 1 to 11 as an active ingredient.

16. A pharmaceutical composition comprising a compound of any one of Claim 1 to 11 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

17. An inhibitor of DPP-IV consisting of a compound of any one of Claim 1 to 11.

18. A method for treatment and/or prevention of NIDDM which comprises administering an effective amount of the compound of any one of Claim 1 to 11 to human beings or animals.

19. The compound of any one of Claim 1 to 11 for use in the treatment and/or prevention of NIDDM in human beings or animals.

20. Use of the compound of any one of Claim 1 to 11 for the manufacture of a medicament for treatment and/or prevention of NIDDM in human beings or animals.

21. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in any one of Claim 1 to 11 and a written matter associated therewith, wherein the written matter states that the

compound (I) can or should be used for preventing or treating NIDDM.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2004/008556

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/06 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/057144 A (WILKINSON DOUGLAS ; WANG ERIC (US); BELYAKOV SERGEI (US); LI WEIXING () 17 July 2003 (2003-07-17) the whole document	1-21
X	US 2001/031780 A1 (CHRISTIANSEN LISE BROWN ET AL) 18 October 2001 (2001-10-18) the whole document	1-21
X	US 6 172 081 B1 (DAMON ROBERT) 9 January 2001 (2001-01-09) the whole document	1-21
P,X	WO 2004/016587 A (ONO PHARMACEUTICAL CO ; KONDO TAKASHI (JP); NAKAI HISAO (JP); YAMAMOTO) 26 February 2004 (2004-02-26) the whole document	1-21

-/--

[X] Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2004/008556

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 308 439 A (WELFIDE CORP) 7 May 2003 (2003-05-07) the whole document -----	1-21

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP2004/008556

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03057144 A	17-07-2003	CA	2471204 A1	17-07-2003
		EP	1465891 A2	13-10-2004
		WO	03057144 A2	17-07-2003
		WO	03057666 A2	17-07-2003
US 2001031780 A1	18-10-2001	US	2002103384 A1	01-08-2002
		AU	2830901 A	07-08-2001
		WO	0155105 A1	02-08-2001
		EP	1254113 A1	06-11-2002
		JP	2003520849 T	08-07-2003
		AU	3362201 A	03-09-2001
		WO	0162266 A2	30-08-2001
		EP	1259246 A2	27-11-2002
		JP	2003523396 T	05-08-2003
		US	2001025023 A1	27-09-2001
US 6172081 B1	09-01-2001	NONE		
WO 2004016587 A	26-02-2004	WO	2004016587 A1	26-02-2004
EP 1308439 A	07-05-2003	AU	7775401 A	25-02-2002
		BR	0113146 A	24-06-2003
		CA	2418656 A1	21-02-2002
		EP	1308439 A1	07-05-2003
		HU	0300746 A2	28-10-2003
		NO	20030619 A	26-02-2003
		NZ	524618 A	27-08-2004
		US	2004106655 A1	03-06-2004
		CN	1441779 T	10-09-2003
		WO	0214271 A1	21-02-2002